

REMARKS

Status of the Claims

Claims 1-6, 8-12, 15-20, 58-77, 79-88, and 90-92 are pending in the application. Claim 14 has been cancelled without prejudice to or disclaimer of the subject matter contained therein. Reexamination and reconsideration of the claims in view of the following comments are respectfully requested.

The Rejections of the Claims under 35 U.S.C. §103 should be Withdrawn

Claims 1, 3-6, 8-12, 14-18, 20, 58-77, 79-88, and 90-92 were rejected under 35 U.S.C. §103(a) as unpatentable over Gnatenko *et al.* (1996, IDS/85), Dwarki *et al.* (U.S. 6,221,646), Dwarki *et al.* (1995, IDS/15), in view of Carter *et al.* (U.S. 5,866,696), Ill *et al.* (U.S. 5,744,326), and evidenced by Vorachek *et al.* (J Bio Chem 2000). This rejection is respectfully traversed.

Gnatenko *et al.* is cited as teaching a recombinant adeno-associated virus vector comprising a B-domain deleted factor VIII linked to a core vWF promoter. The Examiner cites Dwarki *et al.* as teaching a rAAV comprising an AAV ITR, an albumin promoter and an AFP enhancer. The Examiner notes that the vector “could” encode a factor VIII. The Examiner acknowledges that the Gnatenko *et al.* and Dwarki *et al.* references do not teach the use of an AAV ITR as the only promoter expressing a heterologous gene of interest. In fact, in every embodiment described by Dwarki *et al.*, the vector contains heterologous promoter elements (in addition to the ITR) that drive expression of the heterologous gene. While the patent describes the use of an enhancer in a rAAV vector, the enhancer is only used in combination with heterologous promoter elements. Therefore, the references not only fail to teach or suggest the use of an ITR as the only promoter driving expression of a heterologous sequence, but also fail to teach or suggest the combination of the ITR as the only promoter with an enhancer for the expression of B-domain deleted factor VIII as set forth in the claims.

The Examiner cites Carter *et al.* as teaching that the AAV ITR can be used as a transcriptional promoter in an AAV vector carrying a therapeutic gene such as CFTR placed immediately adjacent to the AAV ITR. Ill *et al.* is cited as teaching a hepatitis B enhancer operably linked with a B-domain deleted FVIII. The Examiner then concludes that the ordinary artisan would have been motivated to modify a rAAV vector to use only an AAV ITR as a promoter to drive expression of B-domain deleted factor VIII because it would fall within the bounds of the optimization for those of ordinary skill to make an efficient expression vector, given the teachings in the art regarding various elements making the vector more efficient and suitable for gene therapy,

However, no *prima facie* case of obviousness has been established because there is no motivation or suggestion to combine the cited references. While all the elements of the claims can be found separately in the independent references, the Manual of Patent Examining Procedure (MPEP) explicitly sets forth that there must be a basis in the art for modifying or combining references to support a rejection under 35 U.S.C. § 103. The MPEP provides that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2143.01, citing *In Re: Mills*, 916 F.2d 680, 16 USPQ 2d 1430 (Fed Cir. 1990).

In addition, the Federal Circuit has repeatedly held that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery*, 804 F.2d 135, 140, 231 USPQ 644, 647 (Fed. Cir. 1986). Even if all the elements of a claim are disclosed in various prior art references, the claimed invention taken as a whole cannot be said to be obvious without some reason given in the prior art why one of ordinary skill would have been prompted to combine the teachings of the references to arrive at the claimed invention.

The references must also be viewed without the impermissible hindsight vision afforded by the claimed invention. MPEP § 2141, citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n. 5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). In the present case, it is the Applicants' disclosure of the desirable properties of the vector of claim 1, rather than the prior art, that provides the motivation to one of skill in the art to make such a vector.

The claims require the expression of a B-domain deleted factor using an AAV ITR as the only promoter in combination with an enhancer. None of the cited references teaches nor suggests the claimed invention. In fact, the art teaches away from the claimed invention. As noted in Applicants' previous response, Zhang *et al.* teach that the AAV ITR is a very weak promoter and that a conventional promoter having stronger transcriptional activity than the AAV ITR should be used to drive expression of a transgene. See, for example, the top of column 1 of page 10159 and the middle of column 2 of page 10160 of Zhang *et al.* (1998) *Proc. Natl. Acad. Sci. USA* 95:10158-63, provided as Appendix B with Applicants' amendment mailed March 11, 2003.

Not only did the art fail to suggest the use of the AAV ITR as the only promoter driving expression of a B-domain deleted factor VIII in combination with an enhancer, the art would teach away from the use of the AAV ITR as the only promoter in view of Zhang *et al.* This is particularly true in view of the difficulty of expressing factor VIII, which was widely reported in the art as described in Applicants' response mailed March 11, 2003. For all these reasons, the rejection of the claims under 35 U.S.C. §103 should be withdrawn.

Claims 2 and 19 were rejected under 35 U.S.C. §103(a) as unpatentable over Gnatenko *et al.* (1996), Dwarki *et al.* (U.S. 6,221,646¹), Dwarki *et al.* (1995), Carter *et al.* (U.S. 5,866,696), and Ill *et al.* (U.S. 5,744,326) as applied to the above-referenced claims, and further in view of Gao *et al.* (U.S. 6,258,595). This rejection is respectfully traversed.

Gao *et al.* is cited as teaching to include a DNA spacer in the construct of recombinant AAV vector as an optional element in the design of the vector. However, there is no teaching in Gao *et al.* that the ITR could be used as the only promoter to drive expression of B-domain deleted factor VIII in combination with an enhancer. Furthermore, Gao *et al.* does not provide the motivation to combine the references as noted above. Accordingly, the rejection of claims 2-19 should be withdrawn.

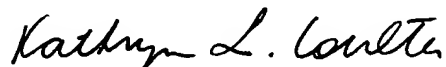
¹ Applicants note that the Dwarki reference is U.S. Patent No. 6,221,646 rather than 6,221,349 as it is listed on page 5 of the Office Action.

CONCLUSIONS

It is believed that the pending claims are patentable over the cited references. Early notice to this effect is solicited. If in the opinion of the Examiner an interview would expedite prosecution, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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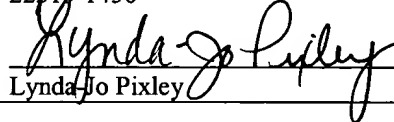
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